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GENERAL CARDIOLOGY

Air pollution and cardiovascular risk in women ► Air pollution has previously been linked to an increased risk of cardiovascular disease. However the mechanism by which this occurs, the magnitude of the association, and the effects of long-term exposure to pollutants remain to be elucidated.

The Women's Health Initiative (WHI) was an observational study of 65 893 post menopausal women in 36 US metropolitan areas that ran from 1994 to 1998 with a median follow-up of 6 years. None of the women recruited had any previous history of cardiovascular disease. Data on air pollution in the cities studied was obtained from the Environmental Protection Agency's Aerometric Information Retrieval System. Each woman's individual exposure to air pollution was estimated by using the monitor closest to their residence. Hazard ratios were estimated for a first cardiovascular event (myocardial infarction, coronary revascularisation, stroke and death from coronary or cerebrovascular disease), adjusting for age, race or ethnic group, smoking status, educational level, household income, body mass index, presence or absence of diabetes, hypertension and hypercholesterolaemia.

Overall 1816 women had one or more fatal or non-fatal cardiovascular events during the four year period of the study. Each increase of 10 μg per cubic metre in levels of particulate matter of less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio (HR), 1.24; 95% confidence interval (CI), 1.09 to 1.41) and a 76% increase in the risk of death from cardiovascular disease (HR, 1.76; 95% CI, 1.25 to 2.47). Risk of cerebrovascular events was also associated with increased levels of $PM_{2.5}$ (HR, 1.35; 95% CI, 1.08 to 1.68).

The exact mechanisms by which fine particulate air pollution exacerbates cardiovascular risk remain to be elucidated. Data show that inhalation of particulate air pollution creates and exacerbates both pulmonary and systemic inflammation and oxidative stress, with a cumulative effect of direct vascular injury, atherosclerosis and autonomic dysfunction. Build up of atherosclerotic plaque, measured by the carotid intima–media thickness is increased in communities with higher mean $PM_{2.5}$ concentrations.

▲ Miller KA, Siscovick DS, Sheppard L, *et al*. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007;**356**:447–58.

▲ Dockery DW, Stone PH. Cardiovascular risks from fine particulate air pollution. *N Engl J Med* 2007;**356**:511–13.

No role for aprotinin in cardiac surgery ► Antifibrinolytic agents have been used to reduce postoperative blood loss and blood transfusion requirements following coronary artery bypass grafting (CABG). These include lysine analogues such as aminocaproic acid and tranexamic acid, and the serine protease inhibitor aprotinin. However, safety concerns have been raised as no long-term mortality data exist in patients given these drugs. This study thus aimed to compare all-cause mortality in patients undergoing CABG according to whether they had been given aminocaproic acid, tranexamic acid, aprotinin, or no anti-bleeding agent.

3876 patients from 62 medical centres were prospectively assessed at 6 weeks, 6 months, and annually for 5 years after CABG surgery. The association between survival and each haemorrhage-sparing medication was compared using multivariable analyses including propensity adjustments. The main outcome measure was death from all causes at five years.

Aprotinin treatment was associated with 223 deaths among 1072 patients (20.8% 5-year mortality) and thus was linked with a significantly increased mortality compared with control (128 deaths among 1009 patients not given any anti-bleeding agents; 12.7%). Neither aminocaproic acid (132 deaths among 834 patients; 15.8%) nor tranexamic acid (65 deaths among 442 patients; 14.7%) was associated with increased mortality. In multivariable logistic regression aprotinin was independently predictive of 5-year mortality among patients with diverse risk profiles, as well as among those surviving their index hospitalisation.

These findings, coupled with previous reports of renal failure and increased cardiovascular event rates, suggest that aprotinin should not be used among patients undergoing CABG surgery when safer and less expensive alternatives are available.

▲ Mangano DT, Miao Y, Vuylsteke A, *et al*. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007;**297**:471–9.

Reducing body iron stores has no effect on incidence of cardiovascular events ► Accumulation of iron in excess of physiological requirements has been postulated to increase the risk of cardiovascular disease through an increase in iron-catalysed free radical-mediated oxidative stress. Therefore could reducing body iron stores by phlebotomy (blood removal) influence the clinical outcomes of patients at high risk of coronary events, namely those with symptomatic peripheral arterial disease (PAD)?

1277 patients from the Iron (Fe) and Atherosclerosis Study (FeAST) with symptomatic but stable PAD were assigned to either reduction of iron stores by phlebotomy at six-monthly intervals (n = 636) or to a control group (n = 641). 99% of the participants were male and 84% were white; the mean age was 67 years. Average follow-up was 4.52 years. The primary end point was all-cause mortality; the secondary end point was death plus non-fatal myocardial infarction and stroke.

In the phlebotomy group, ferritin levels fell from a mean of 121.4 ng/ml at baseline to 79.7 ng/ml. All-cause deaths occurred in 148 patients (23%) in the control group and in 125 (20%) in the iron-reduction group (p = 0.17). Death plus non-fatal myocardial infarction and stroke occurred in 205 patients (32%) in the control group and in 180 (28%) in the iron-reduction group (p = 0.20).

Reduction of body iron stores therefore did not decrease all-cause mortality or death plus non-fatal myocardial infarction and stroke in this population of patients with PAD.

▲ Zacharski LR, Chow BK, Howes PS, *et al*. Reduction of iron stores and cardiovascular outcomes in patients with peripheral arterial disease. *JAMA* 2007;**297**:603–10.

Off-pump CABG does not protect against cognitive impairment ► Advocates of off-pump cardiac surgery suggest morbidity advantages. These are not conclusive in head to head trials with standard surgery. Cognitive impairment following coronary artery bypass grafting (CABG) is a cause of significant morbidity. Does avoiding cardiopulmonary bypass by performing off-pump CABG help to decrease the incidence of cognitive impairment? The Octopus (using the Octopus cardiac stabiliser device) study was a multicentre, randomised controlled trial that enrolled 281 CABG patients between 1998 and 2000. Patients were randomised to receive either off-pump (n = 142) or on-pump (n = 139) surgery. Five years after their surgery, surviving patients were invited for a follow-up assessment. The primary outcome measure was cognitive status as determined by a psychologist, blinded to treatment allocation, who administered 10 standardised neuropsychological tests. A standard definition of cognitive decline was used, which was a 20% decline in performance in 20% of the neuropsycholgical test variables. Secondary measures were occurrence of cardiovascular events (all-cause mortality, stroke, myocardial infarction, and coronary reintervention), anginal status, and quality of life. After five years, cognitive outcomes could be determined in 123 and 117 patients in the off-pump and on-pump groups respectively. 62 (50.4%) of 123 in the off-pump group and 59 (50.4%) of 117 in the on-pump group had cognitive decline ($p > 0.99$). When a more conservative definition of cognitive decline was used, 41 (33.3%) in the off-pump group and 41 (35.0%) in the on-pump group had cognitive decline (p = 0.79). Thirty off-pump patients (21.1%) and 25 on-pump patients (18.0%)

experienced a cardiovascular event (p = 0.55), and no differences were observed in anginal status or quality of life. Therefore in this trial of low-risk CABG patients, avoiding cardiopulmonary bypass had no effect on five-year cognitive or cardiac outcomes.

▲ Van Dijk D, Spoor M, Hijam R, *et al*. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA* 2007;**297**:701–8.

Aspirin-oral anticoagulation combination questioned ► Should aspirin therapy be given to patients already taking warfarin? Dentali *et al*. performed a meta-analysis of randomised controlled trials that compared treatment with warfarin alone versus combined aspirin-warfarin therapy. All trials had at least three months follow-up and the same INR was used in each. In total 10 studies including 4180 patients were analysed. The risk for arterial thromboembolism was lower in patients receiving combined aspirin - oral anticoagulant (OAC) therapy than in those taking OAC alone (odds ratio (OR), 0.66). However, these benefits were limited to patients with a mechanical heart valve (OR, 0.27). There was no difference in the risk for arterial thromboembolism with combined treatment in patients with atrial fibrillation (OR, 0.99), or coronary artery disease (OR, 0.69) and there was no difference in all-cause mortality with either treatment (OR, 0.98). The risk for major bleeding was higher in patients receiving aspirin-OAC therapy compared with OAC therapy alone (OR, 1.43).

Therefore patients on combination therapy do have an increased risk of major bleeding, whereas only those with a mechanical heart valve gain the benefit of a decreased risk of thromboembolism.

▲ Dentali F, Douketis JD, Lim W. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease. *Arch Intern Med* 2007;**167**:117–24.

HDL-C key to statins causing atherosclerosis regression ► What is the relationship between changes in LDL-C, HDL-C, and overall atheroma burden? A post hoc analysis combining raw data from four prospective randomised trials looked at 1455 patients with angiographic coronary disease who underwent serial intravascular ultrasound while receiving statin treatment for 18 months or for 24 months. Statin therapy reduced LDL-C by 23.5% and raised HDL-C by 7.5%. Overall, these changes were accompanied by a mean increase in percentage atheroma volume from 39.7% to 40.1% and a mean decrease in total atheroma volume of 2.4 mm^3 ($p<0.001$). However, substantial atheroma regression (greater than or equal to 5% reduction in atheroma volume) was observed in patients with levels of LDL-C less than the mean (2.25 mmol/l) during treatment and percentage increases of HDL-C greater than the mean (7.5%, $p<0.001$). No significant differences were seen in clinical effects. The findings from this analysis suggest that regression of coronary atherosclerosis requires a substantial reduction in LDL-C and an increase in HDL-C of more than 7.5%. However it remains to be seen whether the atherosclerotic regression associated with these changes in lipid levels will translate into meaningful reductions in clinical events and improved clinical outcomes.

▲ Nicholls SJ, Tuzcu M, Sipahi I, *et al*. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007;**297**:499–508.

ACE and ARB have lowest rates of incident diabetes ► Some antihypertensive drugs can lower glucose tolerance and precipitate diabetes mellitus. Traditional meta-analyses are hindered by heterogeneity across trials and the absence of trials comparing ACE inhibitors with angiotensin-II blockers (ARB). Elliot and Meyer therefore undertook a network meta-analysis, which accounts for both direct and indirect comparisons, to assess the effects of antihypertensive agents on incident diabetes. 22 clinical trials with 143 153 participants who did not have diabetes at randomisation were included. 17 trials enrolled patients with hypertension, three enrolled high-risk patients, and one enrolled those with heart failure. The main outcome was the proportion of patients who developed diabetes. For the drugs analysed, the odds ratio (OR) of developing diabetes was 0.57 for ARB, 0.67 for ACE inhibitors, 0.75 for calcium-channel blockers, 0.77 for placebo and 0.90 for beta-blockers.

Future research should provide more robust data on the glycaemic events of antihypertensive drugs. For example, incident diabetes is a coprimary end point in the ongoing NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial.

▲ Elliot WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007;**369**:201–7.

INTERVENTIONAL CARDIOLOGY

Early or late GP IIb/IIIa in ACS? ► What is the optimal strategy for the use of inhibitors of platelet glycoprotein IIb/IIIa (GP IIa/IIIb) in patients with moderate- and high-risk acute coronary syndromes (ACS) undergoing an early invasive treatment strategy? A total of 9207 patients with moderate- and high-risk ACS undergoing invasive treatment were randomly assigned to receive either routine upstream (n = 4605) or deferred selective (n = 4602) GP IIb/IIIa inhibitor administration. The primary outcome measure was assessment of non-inferiority of deferred GP IIb/IIIa inhibitor use compared with upstream administration for the prevention of composite ischaemic events (death, myocardial infarction, or unplanned revascularisation for ischaemia) at 30 days. Major secondary end points included non-inferiority or superiority of major bleeding and net clinical outcomes (composite ischaemia or major bleeding). GP IIb/IIIa inhibitors were used more frequently (98.3% vs 55.7%) and for a significantly longer duration (median, 18.3 vs 13.1 h) in patients in the upstream group compared with the deferred group. The composite of ischaemic events at 30 days occurred in 7.9% of patients assigned to deferred use compared with 7.1% of patients assigned to upstream administration, and the criterion for non-inferiority was not met. Deferred use compared with upstream use resulted in reduced 30 day rates of major bleeding (4.9% vs 6.1%; p = 0.009 for superiority) and similar rates of net clinical outcomes (11.7% vs 11.7%). Therefore in this trial deferring the use of GPIIa/IIIb inhibitors for selective use in the cardiac catheterisation laboratory resulted in a numerical increase in composite ischaemic events that, while not statistically significant, did not meet the criterion for non-inferiority. However, this finding was offset by a significant reduction in major bleeding. Conclusion? Status quo is preserved for the present—clinical judgement is needed in selecting patients for up-stream use.

▲ Stone GW, Bertrand ME, Moses JW, *et al*. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. *JAMA* 2007;**297**:591–602.

ELECTROPHYSIOLOGY

Increased pulse pressure linked to increased risk of AF ► Increased pulse pressure is a measure of aortic stiffness. It increases cardiac load and may increase the risk of developing atrial fibrillation (AF). To examine the relationship between pulse pressure and incident AF, Mitchell and colleagues followed up 5331 Framingham Heart Study participants aged greater than 35 years. All were free of atrial fibrillation at enrolment and had pulse pressure measured at baseline. Median age was 55 years, and 55% were women. AF developed in 698 participants (13.1%) after a median of 12 years. Cumulative 20-year AF incidence rates were 5.6% for pulse pressure of 40 mm Hg or less (25th centile) and 23.3% for pulse pressure greater than 61 mm Hg (75th centile). After adjustment for standard AF risk factors, pulse pressure was associated with increased risk for AF HR 1.26 per 20 mm Hg increment). Furthermore, this asssociation persisted in models that adjusted for echocardiographic measurements of left atrial dimension. In contrast, mean arterial pressure was unrelated to incident AF. Systolic pressure was related to AF (HR, 1.14 per 20 mm Hg increment); however, if the diastolic pressure was added, the model fit improved and the diastolic relation was inverse (HR, 0.87 per 10 mm Hg increment), consistent with a pulse pressure effect.

Pulse pressure is therefore an important risk factor for the development of AF. The next step is to examine whether interventions that reduce pulse pressure can decrease the incidence of AF.

▲ Mitchell GF, Vasan SR, Keyes MJ, *et al*. Pulse pressure and risk of new-onset atrial fibrillation. *JAMA* 2007;**297**:709–15.

Journals scanned

American Journal of Medicine; American Journal of Physiology: Heart and Circulatory Physiology; Annals of Emergency Medicine; Annals of Thoracic Surgery; Archives of Internal Medicine; BMJ; Chest; European Journal of Cardiothoracic Surgery; Lancet; JAMA; Journal of Clinical Investigation; Journal of Diabetes and its Complications; Journal of Immunology; Journal of Thoracic and Cardiovascular Surgery; Nature Medicine; New England Journal of Medicine; Pharmacoeconomics; Thorax

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